R E M A R K S

Claim 1 was amended by including a feature of claim 4.

Claims 3 and 4 were amended to be consistent with the amended claim 1.

With respect of Rule 116, entry of the above amendments is respectfully requested, since the amendments involve features that were recited in the claims prior to the final rejection.

Applicants' present claims are directed to an ophthalmic solution comprising 0.005% (W/V) latanoprost as an active ingredient, wherein the latanoprost is stabilized to be stored at room temperature by at least one means selected form the following 1) and 2):

1) adjusting the pH of the solution to 5.0 to 6.25 and

2) adding ε-aminocaproic acid to the solution.

In discovering applicants' present claims, the present inventors first focused attention on the physical properties of latanoprost in order to solve the problem that the commercially available latanoprost ophthalmic solution lacks stability. The present inventors conducted various studies and finally discovered a latanoprost ophthalmic solution that can be stored

at room temperature. Specifically, the present inventors discovered that an ophthalmic solution containing 0.005% W/V latanoprost can be stored at room temperature by adjusting the pH of the solution to 5.0 to 6.25 or by adding ε-aminocaproic acid to the solution. That is, applicants' present claims possess a newly achieved advantageous effect that a ophthalmic solution containing 0.005% W/V latanoprost can be stored at room temperature by improving the stability of latanoprost, which has been a problem that has not been able to be solved for many years.

Claims 1 and 2 were rejected under 35 USC 102 as being anticipated by USP 6,011,062 to Schneider et al. for the reasons set forth on pages 2 to 3 of the October 19, 2007 Office Action.

USP 6,011,062 to Schneider et al. (hereinafter referred to as Schneider et al.) describes ophthalmic compositions containing prostaglandin derivatives, and further describes that the prostaglandin derivatives in the compositions are stabilized by adding polyethoxylated castor oil thereto. Moreover, Schneider et al. describe latanoprost as one example of the prostaglandin derivatives. However, Schneider et al. do not describe an

ophthalmic solution comprising 0.005% (W/V) latanoprost, and do not describe at all that the prostaglandin derivatives in a solution are stabilized by adjusting the pH of the solution.

The position was taken in the Office Action that one of ordinary skill in the art would be directed to latanoprost, since members of the prostaglandin derivatives disclosed in Schneider et al. are similar in structure and properties and are limited in number. It was also stated in the Office Action that Schneider et al. teach an ophthalmic composition containing 0.001% (W/V) latanoprost and having a pH of 5.0 to 6.25. Applicants disagree with these contentions for the following reasons.

Schneider et al. describe in Examples 1 and 2 aqueous solutions containing prostaglandin derivatives. In particular, Schneider et al. specifically studied the stability of prostaglandin derivatives contained in the aqueous solutions in Example 1 (see FIGS. 1 to 3). The compound specifically tested by Schneider et al. is Compound 2, and latanoprost was not tested at all by Schneider et al. The position was apparently taken in the Office Action that Compound 2 and latanoprost are prostaglandin derivatives that are similar in structure and properties.

With respect to stability in an aqueous solution, Compound 2 is totally different from latanoprost. In fact, this difference can be clearly seen from FIG. 2 in Schneider et al.

Specifically, "◇" in FIG. 2 of Schneider et al. shows an aqueous solution at a pH of 5.0, but Compound 2 in the aqueous solution is clearly unstable (not stabilized) in view of the fact that the residual ratio of Compound 2 after storage at 55°C for 30 days is below 70%. On the other hand, latanoprost according to applicants' present claims is extremely stable at a pH of 5.0 and the residual ratio of the latanoprost, even after storage at 70°C for 28 days, is approximately 95% (see Table 1 on page 10 of the present specification) . Therefore, the properties of the latanoprost greatly differ from those of the Compound 2 with respect to stability in aqueous solutions.

Accordingly, Compound 2 specifically tested by Schneider et al. is substantially different from latanoprost with regard to physical properties in an aqueous solution. Even though Schneider et al. describe latanoprost as an example of a prostaglandin derivative, since Compound 2 which is described as one of the most preferred examples of prostaglandin derivatives in Schneider

et al. (see Schneider et al., column 6, lines 16 to 21) is not stabilized in the aqueous solution at pH of 5.0, Schneider et al. fail to show that prostaglandin derivatives are stabilized in an aqueous solution at a pH of 5.0. Therefore, the novelty of applicants' present claims, wherein latanoprost is stabilized in an aqueous solution at a pH of 5.0 to 6.25, cannot be denied. That is, Schneider et al. fail to anticipate applicants' present claims, and thus, the novelty rejection is considered to be overcome.

Further, when comparing the degrees of the stability, it is found that applicants' present claims afford a much higher stability than Schneider et al. This is clear from FIG. 1 of Schneider et al.

FIG. 1 in Schneider et al. shows an aqueous solution containing Compound 2 at a concentration of 0.001% (see the two aqueous solutions shown by "O" and "Δ" in FIG. 1 in Schneider et al.). Both of the aqueous solutionsshown by "O" and "Δ" exhibit a stabilizing effect on the prostagrandin derivatives in an aqueous solution only by adding polyethoxylated castor oils. However, the residual ratio of Compound 2 in Schneider et al. is below 60%

after storage at 65°C for 30 days, whereas the residual ratios of latanoprost in the pH-adjusted aqueous solutions according to applicants' present claims are 95% or more after storage at 60°C for 28 days, and 92% or more after storage at 70°C for 28 days, respectively (see Table 1 on page 10 of the present specification). Accordingly, the stabilizing effect afforded by applicants' present claims is clearly higher when compared to that afforded by Schneider et al.

Furthermore, it is respectfully submitted that one of ordinary skill in the art who reads Schneider et al. would be inclined to recognize that prostaglandin derivatives in an aqueous solution at a pH of 5.0 are unstable, because Schneider et al. explicitly describe that Compound 2 in an aqueous solution is unstable at a pH of 5.0. In other words, the description in Schneider et al. teaches away from applicants' present claims wherein latanoprost in an aqueous solution is stabilized by adjusting the pH of the solution to 5.0 to 6.25.

As discussed above, the significant stabilizing effect of applicants' claims are submitted not to be anticipated by Schneider et al., wherein a stabilizing effect according to a pH

adjustment and the stability of latanoprost in an aqueous solution were not actually studied.

In view of the above, withdrawal of the 35 USC 102 rejection is respectfully requested.

Claims 1 to 4 were rejected under 35 USC 103 as being unpatentable (obvious) over USP 6,011,062 to Schneider et al. in view of USP 5,916,550 to Inada et al. for the reasons indicated on pages 3 to 4 of the October 19, 2007 Office Action.

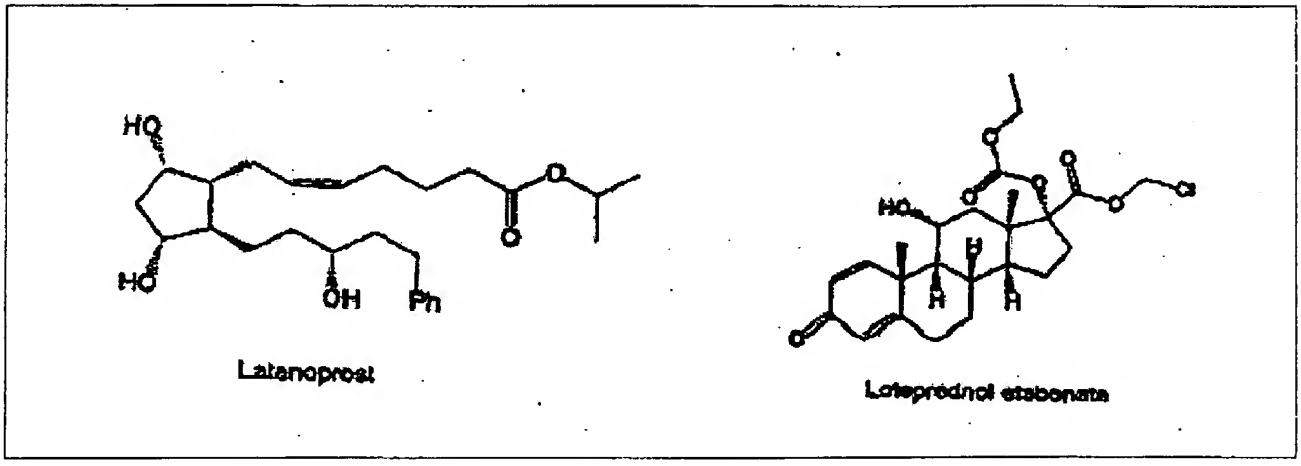
It was admitted in the previous Office Action of July 16, 2007 that Schneider et al. do not teach ε-aminocaproic acid.

As discussed above, applicants' present claims relate to an ophthalmic solution comprising 0.005% (W/V) latanoprost, wherein the latanoprost is stabilized by adjusting the pH of the solution to 5.0 to 6.25 and/or adding ε-aminocaproic acid to the solution.

USP 5,916,550 to Inada et al. (hereinafter referred to as Inada et al.) describe merely a pH depression in an ophthalmic solution comprising loteprednol etabonate ("LE") is restrained by adding ε-aminocaproic acid, which is a buffer. Inada et al. do not specifically describe the stabilization of loteprednol

etabonate. Further, Inada et al. do not even describe latanoprost.

The structural differences between latanoprost and loteprednol etabonate are seen from their structures, which are set forth as follows:



Therefore, it is respectfully submitted that one of ordinary skill in the art would not arrive at applicants' present claims based on Inada et al.

It was pointed out in the October 19, 2007 Office Action that Schneider et al. describe (1) latanoprost as one example of

prostaglandin derivatives and (2) stable ophthalmic compositions containing the prostaglandin derivatives. It was further asserted in the Office Action that Inada et al. describe ophthalmic solutions which (1) control the pH of the solutions by addition of ε-aminocaproic acid and (2) decrease ocular irritation caused by prolonged storage. Moreover, it was concluded in the Office Action that the ophthalmic solution according to applicants' claims was obvious from the combined teachings of Schneider et al. and Inada et al. Applicants' disagree with this conclusion for the following reasons.

First, as discussed above, the prostaglandin derivatives described in Schneider et al. are stabilized by adding polyethoxylated castor oil thereinto and Schneider et al. do not teach or suggest stabilization of prostaglandin derivatives by adjusting the pH to 5.0 to 6.25 and/or adding ε-aminocaproic acid, which are features of applicants' present claims. Further, the prostaglandin derivatives studied by Schneider et al. greatly differ from latanoprost in stability in an aqueous solution. Therefore, just because Schneider et al. name latanoprost as one example of many prostaglandin derivatives, it is respectfully

submitted that it would not be possible to arrive at a stabilized latanoprost ophthalmic solution from Schneider et al. wherein latanoprost was not even actually tested.

Second, what is described as advantages in Inada et al. is that the addition of ε-aminocaproic acid to an ophthalmic solution makes it possible to (1) restrain pH depression in an ophthalmic solution comprising loteprednol etabonate and (2) alleviation of ocular irritation caused by the prolonged storage of the ophthalmic solution. However, regarding the above-mentioned advantage (1), restraint of the pH depression is a naturally obtainable effect when ε-aminocaproic acid, which is a buffer, is added. Moreover, the above-mentioned advantage (2) is irrelevant to the stability with time of loteprednol etabonate in an ophthalmic solution, since alleviation of ocular irritation is due to the fact that an aggregate of loteprednol etabonate, confirmed when adding buffers other than ε-aminocaproic acid, is not confirmed only when adding ε-aminocaproic acid. In other words, Inada et al. do not describe the stabilization of loteprednol etabonate in an ophthalmic solution.

In addition, the ophthalmic solution in Inaba et al. is not an aqueous solution, but a suspension liquid, and the ophthalmic solution of Inada et al. is totally different from that of applicants' present claims with respect to factors contributing to environmental protection and stability. From this viewpoint, Inada et al. fail to teach or suggest the stabilization of loteprednol etabonate.

It is therefore respectfully submitted that a person having ordinary skill in the art would not be able to arrive at applicants' present claims based on the combined teachings of Schneider et al. and Inaba et al., both of which fail to describe or suggest the stabilization of latanoprost in a ophthalmic solution.

At the top of page 4 of the October 19, 2007 Office Action, reference was made to Table 3 of the present specification and it was concluded that the stabilizing effect of latanoprost in an ophthalmic solution by adding ε-aminocaproic acid is not an unexpected effect. Applicants do not agree with this conclusion for the following reason.

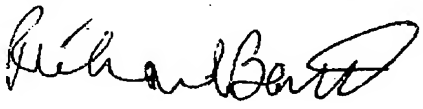
Table 3 of the present specification shows that after storage at 50°C for 8 weeks, the residual ratio of the latanoprost in an ophthalmic solution is 93.1% only when ε-aminocaproic acid is added to the solution. Moreover, Table 3 shows that after storage at 80°C for 4 weeks, the residual ratio of latanoprost is 51.8% when ε-aminocaproic acid is not added, whereas the residual ratio of latanoprost is 6.3 to 28.9% when ε-aminocaproic acid is not added. Thus, applicants' Table 3 clearly shows that the stability of latanoprost in an ophthalmic solution is significantly improved only when ε-aminocaproic acid, out of numerous existing additives, is added.

Withdrawal of the 35 USC 103 rejection is thus respectfully requested.

Reconsideration is requested. Allowance is solicited.

If the Examiner has any comments, questions, objections or recommendations, the Examiner is invited to telephone the undersigned at the telephone number given below for prompt action.

Respectfully submitted,



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